REMARKS

Entry of the foregoing amendment is requested. Claims 173, 174, 176, 179, 181 and 182 are pending.

On September 8, 1999, an Interview Summary of September 7, 1999 was telefaxed to applicants representative. This indicated that an action should be expected by the end of the month. The action did not issue until December 27. Nor did the examiner contact applicants' representative until the end of October. An explanation for the delay following the examiner's precise statement of actions is required.

With respect to the office action, point 1 requires no comment. Point 2 is correct. Point 3 is correct; however, the reason for the commentary is not clear. Applicants have not attempted to rely on a previously filed IDS.

With respect to point 4, while applicants understand that "the current examiner cannot determine what was discussed or agreed upon other than what is in the file application," however, the record includes an "Interview Summary Statement" dated December 22, 1998. Note that this was never mailed to applicants, only telefaxed.

On February 1, 1999, applicants submitted a response in which they stated:

> "It is believed that the Examiner Interview Summary is inaccurate"

Applicants then delineated, in great detail why the summary was inaccurate.

According to MPEP 713.04:

> "Applicant's summary of what took place at the interview should be carefully checked to determine the accuracy of any argument or statement attributed to the examiner during the interview. If there is an inaccuracy and it bears directly on the question of patentability, it should be pointed out in the next office letter."

The next office letter did not dispute applicants' statements. Rather, it was a sequence letter. The names of two of the examiners who participated in the December 23, 1998 interview appear on the

office letter of May 12, 1999.

Another office letter, dated August 31, 1999 issued thereafter. It too, made no mention of applicants' summary.

Over a year later, the present examiner states that he cannot comment on the substance of the interview. With all due respect, personnel who attended the interview remain at the USPTO. Applicants made a prompt response to the Interview Summary, and indicated their disagreement with it. There was ample time for USPTO personnel more familiar with the application and the interview to address the comments made by applicants on February 1. The USPTO cannot excuse its own failure to follow the MPEP by stating that the examiner is no longer present. A complete explanation is needed and is requested.

Referring to point 5A, pages 49-50 have been modified yet again, and a further sequence listing has been provided. As to point 5B, this is addressed infra.

With respect to point 6, the first page of the specification has been amended.

With respect to point 7, a new title is provided, but since the examiner did not specify what is not descriptive, it is not at all certain what was required.

With respect to point 8, a new abstract is provided. Note the comments to point 7, however.

The figure description has been revised.

Duplicate pages have been cancelled.

BALB/C and BALB/c are both used in the literature to describe the mouse strain.

Pages 49 and 50 have been amended to refer to SEQ ID NOS. The examiner has not indicated if and where the omissions occur.

No trademarks are incorrectly named in the application.

With respect to the allegedly defective oath, this can be addressed upon allowance. It will not be addressed here.

The examiner has rejected claims 173, 174, 176, 179, 181 and 182 under 35 USC § 103 in view of Van den Eynde, et al. Int. J. Cancer 44:634-640 (1998) taken with dePlaen, et al, PNAS 85:22 74-2277 (1988) and/or Brown et al, US Patent No. 5,141,742, and/or Seed et al, U.S. Patent No. 5,506,126, "and in further evidence by Van den Bruggen et al Scienc 254:1643-1647 (1991), and Traversari et al, Immunogenetics 35:145-152 (1992)". Having considered this rejection in its

entirety, applicants traverse.

First, applicants point out that claim 176 is entitled to priority of applicants U.S. application Serial no. 807,043, filed December 12, 1991 which is prior to the Van den Bruggen '91 and Traversari '92 papers. Claim 176 reads as follows:

> An isolated, MAGE-1 tumor rejection antigen precursor protein, said protein comprising the amino acid sequence set forth in SEQ ID NO: 26.

SEQ ID NO: 26 is:

Glu Ala Asp Pro Thr Gly His Ser Tyr

This amino acid sequence is encoded by nucleotides 4361-4387 of SEQ ID NO: 8. Review of US Patent No. 5,342,774, which issued from Serial No. 807,043, shows that SEQ ID NO: 8 is presented therein, and is given as MAGE-1 genomic DNA. Nucleotides 4361-4387 are presented in triplet form, indicating that these constitute a coding region. Review of the genetic code, which is a standard feature of molecular biology will prove that the inter region, i.e., nucleotides 4361-4387, must encode SEQ ID NO: 26. Hence, Serial No 807,043 does in fact provide support for an isolated MAGE-1 tumor rejection antigen precursor protein which comprises the amino acid sequence set forth SEQ ID NO: 26. The priority date (December 12, 1991), precedes the publication date of both the Traversari '92 and Van den Bruggen '91 papers. These papers do not constitute prior art, and cannot be used in connection with 35 USC §103.

With respect to the remaining references, one notes that there is a fundamental assumption that underlies the examiner's renaming which is incorrect. According to the examiner:

> "Seed et al teach the rapid immuno selection cloning method for cell surface antigens."

There is no evidence that tumor rejection antigen precursors are cell surface antigens. In fact, they are not.

Tumor rejection antigen precursors do not appear on the surface of cells. Rather, as is well understood by one of the ordinary skill in the art – and is explained at great length in the specification – tumor rejection antigen precursors are processed, intracellularly, into tumor rejection antigens, which associate, intracellularly, with MHC molecules. The resulting complexes are expressed on cells. The parental, tumor rejection antigen precursor, is not.

The examiner points to the identification of "antigen E" in the art. "Identification" may be too strong a term for what was known of antigen E prior to the filing of applicants' application. "Antigen E" was known via its recognition by certain CTLs, and lack of recognition by others. Its amino acid sequence was not known. The parent molecule from which it was derived was not known.

The Brown molecule, i.e., the tumor antigen (and there is only one, contrary to the examiner's contention that Brown teaches tumor antigens), is a cell surface antigen. Brown so states. The examiner has, again, made an assumption that is not correct - i.e., that the isolation and cloning of techniques applicable to cell surface molecules is applicable to those molecules which are not found on cell surfaces. Brown states quite clearly that the antigen in question is expressed in both normal and neoplastic tissues. See column 3, line 32. Also, Brown provides the amino acid sequence of the p97 antigen (see figures 3A and 3B), and there is no sequence therein which corresponds to the sequences claimed. There is no evidence that p97 is processed into peptides that are presented by MHC or HLA molecules. One simply cannot equate the teachings of Brown to what is claimed, or carry out any of the extrapolation that the examiner has.

With respect to the Seed reference, ab initio applicants question the prior art status of the patent. The application has a priority date which predates the filing date of the Seed patent by nearly a year. Seed is entitled to a priority date of December 1, 1992. It is a continuation in part of an earlier application, and the examiner has not established that the Seed '126 patent is entitled to claim relevant priority from the 1990 filing date.

Further, the Seed patent is clearly directed to cell surface antigens, large enough to stimulate antibodies, which are found on normal cells. Preexisting antibodies are necessary to carry out Seed's invention. There is no evidence that the claimed molecule was known to the art. Nor are applicants' claiming cDNA molecules, nucleic acid molecules of any type, or methodologies for isolating such molecules. This is the subject matter to which the Seed reference is directed.

One is hard pressed to see how these disclosures are relevant to what is claimed, or the molecules to combine them with the remaining references.

The examiner states of Van den Eynde that it:

> "teach(es) the presence and identification of human melanoma antigens recognized by cytotoxic T lymphocytes, including antigen

E and its prospects for immunotherapy."

Actually Van den Eynde discloses how autologous CTLs recognized various antigens, as presented by various sublines of a melanoma cell line. It is well known that CTLs recognize complexes of peptides and HLA molecules. They do not recognize complete molecules, such as tumor rejection antigen precursors. CTLs recognize tumor rejection antigens. From the Van den Eynde reference, it is not possible to tell if one, two, six, or an undefined number of different tumor rejection antigen precursors are processed to the six apparently different tumor rejection antigens. The skilled artisan could not draw the conclusions drawn by the examiner without hindsight - indeed, both Van den Bruggen and Traversari are NOT prior art. Further, the examiner states that these references teach that

> "the antigen associated with the 2.4 kb fragment disclosed in Example 20 of the specification and encompassed by the claimed invention is the same antigen E disclosed in Van den Eynde et al."

Neither reference so states. "Antigen E" is a tumor rejection antigen, it is not a tumor rejection antigen precursor.

It is not understood why the DePlaen reference is relied upon. The examiner states that

> "DePlaen et al teach the same cloning of tumor antigens as disclosed."

Not so. DePlaen et al deals with tum-variant P91A. As is clearly defined in the specification, P91A is NOT a tumor rejection antigen precursor as claimed. The examiner is directed to page 6, lines 3-18 of the specification, e.g., for a discussion of the tum–antigens. Lines 15-18, in particular, distinguish the tumor rejection antigen precursors from molecules such as P91A, and render the DePlaen reference inappropriate to what is claimed.

As shown herein, one of ordinary skill in the art cannot arrive at the claimed invention without the use of improper hindsight reconstruction. As such, the rejection should be withdrawn.

A rejection is set forth at point 14, i.e., the examiner has rejected claims 176 and 182 under 35 USC §112, second paragraph, as allegedly being indefinite, in view of the use of the term "stringent conditions."

According to the examiner:

> "The term in a claim is a relative term which renders the claim indefinite. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably appraised of the metes and bounds of the invention."

The examiner's attention is directed to the conditions, which are set forth at page 47, line 20 - page 48, line 7. Immediately thereafter, the following is set forth:

> "In the following examples, whenever 'hybridization' is referred to, the stringency conditions used were similar to those described supra 'stringent conditions' as used herein thus refers to the foregoing conditions; subject to routine, art recognized modification."

There is a clear definition set forth in the specification, with ample guidance. The rejection is improper, and should be withdrawn.

Point 13 sets out an objection to an amendment, arguing that it sets forth new matter. The examiner argues that in presenting corrected sequence information, applicants submitted new matter. After summarizing a declaration which applicants submitted, the examiner states that:

> "In contrast to applicant's assertions or new matter, the following is noted."

This statement is not understood. The syntax is not correct, and applicants made no assertions as to "new matter." Hence, it is not clear what the examiner intends.

The examiner then states that applicants disclose a 2.4 kb and a 1.8 kb fragment, and not a 1.7 kb or a 1.3 kb fragment, nor a 1.7 kb plus 10 base pair cDNA molecule.

In response, applicants direct the examiner's attention to point "3" of the declaration attached hereto. The specifications refer to a cDNA molecule where a weight of 1.8 kb was determined by blotting. By sequencing, this molecule was 1,690 nucleotides long. It was the same molecule.

With respect to the alleged failure to describe a 1.3 kb cDNA molecule and one of 1.7 kb + 10 nucleotides in length, this is irrelevant. The issue is: what is the correct sequence of the molecule disclosed? In their declaration, applicants explain how this was determined. The examiner has not

explained how the alleged failure to disclose this information is at all relevant.

The examiner then argues that the second cDNA library described in the declaration is not described in the specification. Again, the relevance of this alleged failure is not understood. Applicants are not "relying" on the second library. Again, what is relevant is the correct sequence for what is disclosed. The second library was used to determine this. Sequence information is inherent in a molecule. Ex parte Gray. Applicants are providing what is inherent.

The examiner then argues that:

> "There is unpredictability that a second cDNA library relied upon by applicant to change sequences would be necessarily the same as the first cDNA library disclosed in the specification as filed. Further there is insufficient objective evidence that the sequence now relied upon by applicant was based upon either the 2.4 kb fragment and a 1.8 kb fragment which were disclosed in the specification as filed. Also, it is well known that enzymes used in making a cDNA from mRNA library are prone to error incorporating the wrong nucleotides (see Richetti et al EMBO J 9:1583-1593 (1990); see entire document, including Abstract). It is not clear that the difference of the missing nucleotide 'C' is a result of a compression, as set forth by the declaration."

The sequence relied upon by applicants is based upon both the 2.4 kb fragment and the 1.8/1.7 kb fragment. As is elaborated in the attached declaration, the facts are the following. Applicants had estimated the size of the relevant molecule by blotting. They knew that a cDNA molecule that was 1.3 kb long was not sufficient. They then began sequence work, using the 2.4 kb, genomic clone. They also sequenced the incomplete molecule i.e., the 1.3 kb cDNA clone. Following this, the 1.3 kb cDNA clone was used as a probe, and the 1.8 (Northern blotting)/1.7 (by sequencing) cDNA molecule was identified, and sequenced. As the declaration reports, the antisense molecule was sequenced, for both the 2.4 kb and 1.7 kb molecules. These were consistent with each other, but inconsistent with the 1.3 kb cDNA molecule. Note that the 1.3 kb molecule was sequenced on the sense strand, rather than the antisense strands, for the 2.4 kb and 1.8/1.7 kb molecules.

A second cDNA library was prepared for collaborators. This resulted in, inter alia, a clone that was 1.7 kb + 10 nucleotides long. Note that the collaborators sequenced the sense strand of the

molecule. This was identical to the relevant sequence over the 1.3 kb molecule. When the inventors sequenced the 1.7 kb + 10 molecule – on both strands – they found a disparity, i.e., the sense strand was identical to that of their collaborators, and differed from the sequence information from the antisense strand. The antisense strand sequence lacked a nucleotide, and was identical to the antisense strand for the 2.4 kb and 1.8/1.7 kb strands.

Clearly, the molecule sent to the collaborators, i.e., the 1.7 + 10 kb molecule, encoded the same molecule as is described in the specification, and claimed. How, else, can one explain the fact that all three antisense strands were identical, and the identity of sequence information in the sense strands?

The examiner argues that "it was well known that enzymes used in making a cDNA from mRNA library are prone to error incorporating the wrong nucleotides," citing to Richetti, et al., EMBO J 9: 1583-1593 (1990). As applicants point out at paragraph "14" of the declaration, the identity over the sense strand strongly suggests that the problem discussed by Richetti was not an issue here. Applicants clearly included safeguards that Richetti did not, in order to determine what the correct sequence of the molecule was.

The examiner has included additional statements, for reasons that are not clear. For example:

> "It is noted applicant appears to have corrected a sequence or obtain (sic) a new sequence in 1993; (sic) but did not disclose either in the instant application USSN 08/819,669 filed 3/17/97, nor in the parent application USSN 08/142, 368 filed 5/2/94 at the time of filing either application."

With respect to this statement, Serial No. 08/142,368 was drawn to a peptide. The correction of the nucleotide sequence herein has no bearing on the peptide claimed in 08/142,368. The correction was not made at the time of filing because applicants believe – and maintain their belief – that the change in SEQ ID NO: 8 is not material to what is claimed. The claims are drawn to tumor rejection antigen precursors. As explained in the specification, tumor rejection antigen precursors are processed to tumor rejection antigens - such as the peptide of SEQ ID NO: 26. This "TRA" is unchanged in the corrected sequence. The molecule remains a tumor rejection antigen precursor.

The examiner states as well that:

> "Applicant also is claiming generally tumor

> rejection antigen precursor encoded by nucleotide sequences that hybridize to SEQ ID NO: 8; therefore the claims are not limited to specific sequences set forth either in the claims or in the instant disclosure."

Apparently, the examiner feels that the difference in one nucleotide somehow renders this language unacceptable.

The examiner is called upon to show how the difference in one nucleotide renders it impossible for the skilled artisan to find molecules that hybridize to either the correct or incorrect sequence, and encode tumor rejection antigen precursors. As was explained, supra, SEQ ID NO: 26 is a tumor rejection antigen. It clearly resulted from the cDNA molecule described in the application. The TRA did not change. Review of the art in this area will show many TRAs which are derived from SEQ ID No: 8 that are not affected by the sequence change.

There is no "limitation" recited in the claims "nor clearly disclosed" in the specification which "introduce new concepts" and "violate" the description requirement of the first paragraph of 35 U.S.C. 112. What "limitation" is recited that is not described originally? What "new concept" is introduced? The examiner is called upon to state this with specificity.

Attached hereto is a declaration by all of the inventors. The declaration explains, as is pointed out, supra, that a molecule determined to be 1.8 kb in size via Northern blotting can be 1.7 kb long when actually sequenced.

Further, this declaration explains that the inventors have frozen samples of the original clones which were sequenced when the application was filed originally. The declaration explains how one of the inventors, Dr. Pierre van der Bruggen, prepared and labelled frozen samples of E.coli cells which contained, as a recombinant insert, either the 1.7 kb cDNA molecule, or the 1.3 kb cDNA molecules.. By reviewing his laboratory notebooks, prepared when he first sequenced the 1.7 kb and 1.3 kb cDNA molecules, Dr. van der Bruggen was able to identify frozen samples containing inserts identical to those he had sequenced previously. The declaration goes on to explain that the frozen samples were thawed, and that the inserts were removed and sequenced. When the inserts were sequenced, it was determined that each contained the "C" base that was not included when the sequence information was provided originally.

The same clones were used. Clearly there was an error in the first submission. The nucleotide sequence of a given cDNA molecule is inherent to that molecule. It does not change.

Hence, applicants are simply correcting an error so that the inherent properties of the sequence are presented. This information establishes, clearly and without ambiguity, that the correction of the sequences does NOT constitute new matter.

Applicants representative discussed this declaration with Group Director John Doll, who indicated that a declaration which showed that the original materials upon resequencing contained the additional base, would be sufficient to obviate the pending new matter objection. As such, if this declaration does NOT obviate the objection, applicants request a telephone interview at which Mr. Doll participates.

Applicants have pointed out that they are correcting an error in an inherent property of a molecule described in the application. There is no new matter, and nothing to cancel.

All points have been addressed, and answered. Withdrawal of all rejections, and allowance of this application is believed proper, and is urged.

Respectfully submitted,

FULBRIGHT & JAWORSKI L.L.P.

By _____
Norman D. Hanson
Reg. No. 30,946

666 Fifth Avenue
New York, New York 10103
(212) 318-3000